

## 4. INTRODUCTION

### 4.1 Investigational Plan

Vical Inc. proposes to combine Allovectin-7 and Leuvectin in a Phase I protocol to assess safety by intratumoral administration in late-stage melanoma patients. This combination approach is intended to stimulate an immune response by expressing HLA-B7 antigen within the tumor, potentially restoring some degree of major histocompatibility complex (MHC) class I tumor antigen presentation, and expressing interleukin-2 (IL-2) within the tumor to further expand stimulated specific T cells.

### 4.2 Overview

The management of malignant melanoma remains unsatisfactory. In recent years the incidence of malignant melanoma has been doubling approximately every 10 years (1). Even with generous surgical margins and regional lymphadenectomy, many lesions will recur (2,3). High dose interferon  $\alpha$  can reduce recurrence in Stage I and II melanoma by about 40%, but it is associated with significant toxicity (4). There is continuing effort to identify other approaches, such as immunotherapy, that might lend themselves to adjuvant use.

Dimethyl triazeno imidazole carboxamide (DTIC) is the best single chemotherapy agent with a response rate in systemic, metastatic disease of about 20% (5). Significantly increased response rates can be expected with newer combination programs such as tamoxifen, BCNU, cis-platinum and DTIC (6), but this is at the cost of increased toxicity. There is no consensus on second line treatment, and no treatment after front-line therapy for Stage III and IV disease has been shown to be effective. At this point, consideration is often given to the use of cytokines or other experimental approaches.

The role of the immune system in malignant melanoma has been an area of intense interest. Melanoma antigens have been well studied in the past, as has evidence of a host immune response (6-8). Agents that can stimulate non-HLA-restricted cellular cytotoxicity, such as interferons and interleukin-2, have produced sustained regressions in some patients (9).

It is now possible to trigger an immune response through gene transfer. Numerous models have been developed and have led to several clinical trials exploring the possibility of manipulating either tumor cells or host lymphocytes transfected with a variety of cytokine genes (10). Other specific gene therapy strategies have sought to directly influence the interaction between immunocyte and antigen presenting cell by enhancement of HLA-restricted immunity.

## 5. BACKGROUND AND RATIONALE

### 5.1 Allovectin-7

Allovectin-7 is a direct gene therapy product developed by Vical Inc. which contains the gene for the highly immunogenic MHC class I transplantation antigen, HLA-B7. It is administered by direct intratumoral injection. The product contains plasmid DNA, VCL-1005, which encodes the HLA-B7 heavy chain and  $\beta$ 2 microglobulin proteins. The  $\beta$ 2 microglobulin allows synthesis and expression of the complete MHC complex on the cell surface (11).

### 5.2 Leuvectin

Leuvectin is a direct gene therapy product developed by Vical Inc. which contains plasmid DNA, VCL-1102, that encodes the IL-2 protein. The plasmid is complexed with the cationic lipid mixture, DMRIE/DOPE, and is administered by intratumoral injection.

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